	Type	L #	Hits	Search Text	DBs	Time Stamp	Comments	Error Definition	Errors
1	BRS	L1	2925	(alternative adj splicing adj factor) or asf	US-PGPUB; USPAT; EPO; JPO; DERWENT	2005/02/11 07:28			
2	BRS	L2	1615	aberrant adj splicing	US-PGPUB; USPAT; EPO; JPO; DERWENT	2005/02/11 07:29			
3	BRS	L3	2	1 same 2	US-PGPUB; USPAT; EPO; JPO; DERWENT	2005/02/11 07:29			
4	BRS	L4	2	1 same 2 same disease	US-PGPUB; USPAT; EPO; JPO; DERWENT	2005/02/11 07:29			
5	BRS	L5	14081	cystic adj fibrosis	US-PGPUB; USPAT; EPO; JPO; DERWENT	2005/02/11 07:30			
6	BRS	L6	174	(exon adj inclusion) or (exon adj skipping)	US-PGPUB; USPAT; EPO; JPO; DERWENT	2005/02/11 07:31			
7	BRS	L7	1407	(2 or 6) same disease	US-PGPUB; USPAT; EPO; JPO; DERWENT	2005/02/11 07:32			
8	BRS	L8	161	SR adj protein	US-PGPUB; USPAT; EPO; JPO; DERWENT	2005/02/11 07:32			
9	BRS	L9	47	(heterogeneous adj nuclear adj ribonucleoprotein adj a1) or hbrnpa1	US-PGPUB; USPAT; EPO; JPO; DERWENT	2005/02/11 07:32			
10	BRS	L10	49	E4-ORF3 or E4-ORF6	US-PGPUB; USPAT; EPO; JPO; DERWENT	2005/02/11 07:33			
11	BRS	L11	2	7 same (1 or 8 or 9 or 10)	US-PGPUB; USPAT; EPO; JPO; DERWENT	2005/02/11 07:34			
12	BRS	L12	15	5 same (2 or 6)	US-PGPUB; USPAT; EPO; JPO; DERWENT	2005/02/11 07:34			
13	BRS	L13	1	12 same (1 or 8 or 9 or 10)	US-PGPUB; USPAT; EPO; JPO; DERWENT	2005/02/11 07:35			

	Type	L #	Hits	Search Text	DBs	Time Stamp	Comments	Error Definition	Errors
14	BRS	L14	1	kerem adj batsheva.in.	US-PGPUB; USPAT; EPO; JPO; DERWENT	2005/02/11 07:35			

=> d his

(FILE 'HOME' ENTERED AT 07:38:02 ON 11 FEB 2005)

FILE 'MEDLINE, CAPLUS, BIOSIS, EMBASE, SCISEARCH, AGRICOLA' ENTERED AT
07:38:25 ON 11 FEB 2005
L1 3729 S (ALTERNATIVE SPLICING FACTOR) OR ASF
L2 3377 S SR PROTEIN
L3 447 S (HETEROGENEOUS NUCLEAR RIBONUCLEOPROTEIN A1) OR HBRNPA1
L4 220 S E4-ORF3 OR E4-ORF6
L5 7007 S L1 OR L2 OR L3 OR L4
L6 2113 S ABERRANT SPLICING
L7 3455 S (EXON INCLUSION) OR (EXON SKIPPING)
L8 5398 S L6 OR L7
L10 103175 S CYSTIC FIBROSIS
L11 19 S L5 (P) L8 (P) L10
L12 4 DUPLICATE REMOVE L11 (15 DUPLICATES REMOVED)
L13 43 S L5 (P) L8 (P) DISEASE
L14 9 DUPLICATE REMOVE L13 (34 DUPLICATES REMOVED)
L15 6 S L14 NOT L12
L16 389 S KEREM B?/AU
L17 8 S L16 AND L8
L18 4 DUPLICATE REMOVE L17 (4 DUPLICATES REMOVED)
L19 7 S L16 AND L5
L20 3 DUPLICATE REMOVE L19 (4 DUPLICATES REMOVED)
L21 5 S L18 OR L20

=> log y

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FILE 'MEDLINE' ENTERED AT 07:38:25 ON 11 FEB 2005

FILE 'CAPLUS' ENTERED AT 07:38:25 ON 11 FEB 2005
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
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FILE 'AGRICOLA' ENTERED AT 07:38:25 ON 11 FEB 2005

=> s (alternative splicing factor) or asf
L1          3729 (ALTERNATIVE SPLICING FACTOR) OR ASF

=> s sr protein
L2          3377 SR PROTEIN

=> s (heterogeneous nuclear ribonucleoprotein a1) or hbrnpa1
L3           447 (HETEROGENEOUS NUCLEAR RIBONUCLEOPROTEIN A1) OR HBRNPA1

=> s e4-orf3 or e4-orf6
L4           220 E4-ORF3 OR E4-ORF6

=> s l1 or l2 or l3 or l4
L5          7007 L1 OR L2 OR L3 OR L4

=> s aberrant splicing
L6          2113 ABERRANT SPLICING

=> s (exon inclusion) or (exon skipping)
L7          3455 (EXON INCLUSION) OR (EXON SKIPPING)

=> s l6 or l7
L8          5398 L6 OR L7

=> s cyctic fibrosis
L9            20 CYCTIC FIBROSIS

=> s cystic fibrosis
L10       103175 CYSTIC FIBROSIS

=> s l5 (p) l8 (p) l10
L11           19 L5 (P) L8 (P) L10

=> duplicate remove l11
DUPLICATE PREFERENCE IS 'MEDLINE, CAPLUS, BIOSIS, EMBASE, SCISEARCH'
KEEP DUPLICATES FROM MORE THAN ONE FILE?  Y/(N):n
PROCESSING COMPLETED FOR L11
L12            4 DUPLICATE REMOVE L11 (15 DUPLICATES REMOVED)

=> d l12 1-4 ibib abs

L12  ANSWER 1 OF 4     MEDLINE on STN                    DUPLICATE 1
ACCESSION NUMBER:    2003399621     MEDLINE
DOCUMENT NUMBER:     PubMed ID: 12913074
TITLE:               Characterization of disease-associated mutations affecting
                     an exonic splicing enhancer and two cryptic splice sites in
                     exon 13 of the cystic fibrosis transmembrane conductance
                     regulator gene.
AUTHOR:              Aznarez Isabel; Chan Elayne M; Zielenski Julian; Blencowe
                     Benjamin J; Tsui Lap-Chee
CORPORATE SOURCE:    Genetics and Genomics Biology Program, The Hospital for
                     Sick Children, Toronto, Canada, M5G 1X8.
CONTRACT NUMBER:     P50 DK49096-9 (NIDDK)
SOURCE:              Human molecular genetics, (2003 Aug 15) 12 (16) 2031-40.
                     Journal code: 9208958. ISSN: 0964-6906.
PUB. COUNTRY:        England: United Kingdom
DOCUMENT TYPE:       Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:            English
```

FILE SEGMENT: Priority Journals
ENTRY MONTH: 200405
ENTRY DATE: Entered STN: 20030827
Last Updated on STN: 20040521
Entered Medline: 20040520

AB Sequences in exons can play an important role in constitutive and regulated pre-mRNA splicing. Since exonic splicing regulatory sequences are generally poorly conserved and their mechanism of action is not well understood, the consequence of exonic mutations on splicing can only be determined empirically. In this study, we have investigated the consequence of two ***cystic*** ***fibrosis*** (CF) disease-causing mutations, E656X and 2108delA, on the function of a putative exonic splicing enhancer (ESE) in exon 13 of the CFTR gene. We have also determined whether five other CF mutations D648V, D651N, G654S, E664X and T665S located near this putative ESE could lead to ***aberrant*** ***splicing*** of exon 13. Using minigene constructs, we have demonstrated that the E656X and 2108delA mutations could indeed cause ***aberrant*** ***splicing*** in a predicted manner, supporting a role for the putative ESE sequence in pre-mRNA splicing. In addition, we have shown that D648V, E664X and T665S mutations could cause ***aberrant*** ***splicing*** of exon 13 by improving the polypyrimidine tracts of two cryptic 3' splice sites. We also provide evidence that the relative levels of two splicing factors, hTra2alpha and SF2/ ***ASF*** , could alter the effect on splicing of some of the exon 13 disease mutations. Taken together, our results suggest that the severity of CF disease could be modulated by changes in the fidelity of CFTR pre-mRNA splicing.

L12 ANSWER 2 OF 4 MEDLINE on STN DUPLICATE 2
ACCESSION NUMBER: 2001229125 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11285240
TITLE: Nuclear factor TDP-43 and SR proteins promote in vitro and in vivo CFTR exon 9 skipping.
AUTHOR: Buratti E; Dork T; Zuccato E; Pagani F; Romano M; Baralle F E
CORPORATE SOURCE: International Centre for Genetic Engineering and Biotechnology (ICGEB), Padriciano 99, 34012 Trieste, Italy.
SOURCE: EMBO journal, (2001 Apr 2) 20 (7) 1774-84.
Journal code: 8208664. ISSN: 0261-4189.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200106
ENTRY DATE: Entered STN: 20010611
Last Updated on STN: 20010611
Entered Medline: 20010607

AB Alternative splicing of human ***cystic*** ***fibrosis*** transmembrane conductance regulator (CFTR) exon 9 is regulated by a combination of cis-acting elements distributed through the exon and both flanking introns (IVS8 and IVS9). Several studies have identified in the IVS8 intron 3' splice site a regulatory element that is composed of a polymorphic (TG)m(T)n repeated sequence. At present, no cellular factors have been identified that recognize this element. We have identified TDP-43, a nuclear protein not previously described to bind RNA, as the factor binding specifically to the (TG)m sequence. Transient TDP-43 overexpression in Hep3B cells results in an increase in exon 9 skipping. This effect is more pronounced with concomitant overexpression of ***SR*** ***proteins*** . Antisense inhibition of endogenous TDP-43 expression results in increased inclusion of exon 9, providing a new therapeutic target to correct ***aberrant*** ***splicing*** of exon 9 in CF patients. The clinical and biological relevance of this finding in vivo is demonstrated by our characterization of a CF patient carrying a TG10T9(DeltaF508)/TG13T3(wt) genotype leading to a disease-causing high proportion of exon 9 skipping.

L12 ANSWER 3 OF 4 MEDLINE on STN DUPLICATE 3
ACCESSION NUMBER: 2000396647 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10766763
TITLE: Splicing factors induce cystic fibrosis transmembrane regulator exon 9 skipping through a nonevolutionary conserved intronic element.
AUTHOR: Pagani F; Buratti E; Stuani C; Romano M; Zuccato E; Niksic M; Giglio L; Faraguna D; Baralle F E
CORPORATE SOURCE: International Centre for Genetic Engineering and Biotechnology, Padriciano 99 and IRCCS, Burlo Garofolo, via dell'Istria 65/1, Trieste, TS 34012 Italy.

SOURCE: Journal of biological chemistry, (2000 Jul 14) 275 (28) 21041-7.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200008
ENTRY DATE: Entered STN: 20000824
Last Updated on STN: 20000824
Entered Medline: 20000816

AB In monosymptomatic forms of ***cystic*** ***fibrosis*** such as congenital bilateral absence of vas deferens, variations in the TG(m) and T(n) polymorphic repeats at the 3' end of intron 8 of the ***cystic*** ***fibrosis*** transmembrane regulator (CFTR) gene are associated with the alternative splicing of exon 9, which results in a nonfunctional CFTR protein. Using a minigene model system, we have previously shown a direct relationship between the TG(m)T(n) polymorphism and exon 9 splicing. We have now evaluated the role of splicing factors in the regulation of the alternative splicing of this exon. Serine-arginine-rich proteins and the ***heterogeneous*** ***nuclear*** ***ribonucleoprotein*** ***A1*** induced ***exon*** ***skipping*** in the human gene but not in its mouse counterpart. The effect of these proteins on exon 9 exclusion was strictly dependent on the composition of the TG(m) and T(n) polymorphic repeats. The comparative and functional analysis of the human and mouse CFTR genes showed that a region of about 150 nucleotides, present only in the human intron 9, mediates the exon 9 splicing inhibition in association with exonic regulatory elements. This region, defined as the CFTR exon 9 intronic splicing silencer, is a target for serine-arginine-rich protein interactions. Thus, the nonevolutionary conserved CFTR exon 9 alternative splicing is modulated by the TG(m) and T(n) polymorphism at the 3' splice region, enhancer and silencer exonic elements, and the intronic splicing silencer in the proximal 5' intronic region. Tissue levels and individual variability of splicing factors would determine the penetrance of the TG(m)T(n) locus in monosymptomatic forms of ***cystic*** ***fibrosis*** .

L12 ANSWER 4 OF 4 MEDLINE on STN DUPLICATE 4
ACCESSION NUMBER: 2001014733 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10915765
TITLE: Cellular and viral splicing factors can modify the splicing pattern of CFTR transcripts carrying splicing mutations.
AUTHOR: Nissim-Rafinia M; Chiba-Falek O; Sharon G; Boss A; Kerem B
CORPORATE SOURCE: Department of Genetics, Life Sciences Institute, The Hebrew University, Jerusalem 91904, Israel.
SOURCE: Human molecular genetics, (2000 Jul 22) 9 (12) 1771-8.
Journal code: 9208958. ISSN: 0964-6906.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200010
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20021218
Entered Medline: 20001027

AB Variable levels of aberrantly spliced ***cystic*** ***fibrosis*** transmembrane conductance regulator (CFTR) transcripts were suggested to correlate with variable ***cystic*** ***fibrosis*** (CF) severity. We studied the effect of the cellular splicing factors, hnRNP A1 and ***ASF*** /SF2, and their adenoviral analogues, ***E4*** - ***ORF6*** and ***E4*** - ***ORF3*** , that promote ***exon*** ***skipping*** and/or ***exon*** ***inclusion*** , on the splicing pattern of the CFTR mutation 3849+10kb C-->T and the 5T allele. These mutations can lead to cryptic ***exon*** ***inclusion*** and ***exon*** ***skipping*** , respectively. Overexpression of the cellular factors promoted ***exon*** ***skipping*** of pre-mRNA transcribed from minigenes carrying the mutation (p5T or p3849M). This led to a substantial decrease in the level of correctly spliced mRNA transcribed from p5T and generated correctly spliced mRNA transcribed from p3849M that was not found without overexpression of the factors. The viral factor, ***E4*** - ***ORF3*** , promoted ***exon*** ***inclusion*** and led to a substantial increase of the correctly spliced mRNA transcribed from the p5T. The factor, ***E4*** - ***ORF6*** , activated ***exon*** ***skipping*** and generated correctly spliced mRNA transcribed from p3849M. Thus, overexpression of ***alternative*** ***splicing*** ***factors*** can modulate the splicing pattern of CFTR alleles carrying splicing mutations. These

results are important for understanding the mechanism underlying phenotypic variability in CF and other genetic diseases.

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=> d his

     (FILE 'HOME' ENTERED AT 07:38:02 ON 11 FEB 2005)

     FILE 'MEDLINE, CAPLUS, BIOSIS, EMBASE, SCISEARCH, AGRICOLA' ENTERED AT
     07:38:25 ON 11 FEB 2005
L1          3729 S (ALTERNATIVE SPLICING FACTOR) OR ASF
L2          3377 S SR PROTEIN
L3           447 S (HETEROGENEOUS NUCLEAR RIBONUCLEOPROTEIN A1) OR HBRNPA1
L4           220 S E4-ORF3 OR E4-ORF6
L5          7007 S L1 OR L2 OR L3 OR L4
L6          2113 S ABERRANT SPLICING
L7          3455 S (EXON INCLUSION) OR (EXON SKIPPING)
L8          5398 S L6 OR L7
L9            20 S CYCTIC FIBROSIS
L10       103175 S CYSTIC FIBROSIS
L11           19 S L5 (P) L8 (P) L10
L12            4 DUPLICATE REMOVE L11 (15 DUPLICATES REMOVED)

=> s l5 (p) l8 (p) disease
L13           43 L5 (P) L8 (P) DISEASE

=> duplicate remove l13
DUPLICATE PREFERENCE IS 'MEDLINE, CAPLUS, BIOSIS, EMBASE, SCISEARCH'
KEEP DUPLICATES FROM MORE THAN ONE FILE?  Y/(N):n
PROCESSING COMPLETED FOR L13
L14            9 DUPLICATE REMOVE L13 (34 DUPLICATES REMOVED)

=> s l14 not l12
L15            6 L14 NOT L12

=> d l15 1-6 ibib abs

L15  ANSWER 1 OF 6     MEDLINE on STN
ACCESSION NUMBER:    2004603724     IN-PROCESS
DOCUMENT NUMBER:     PubMed ID: 15496424
TITLE:               Branch site haplotypes that control alternative splicing.
AUTHOR:              Kralovicova Jana; Houngninou-Molango Sophie; Kramer Angela;
                     Vorechovsky Igor
CORPORATE SOURCE:    University of Southampton School of Medicine, Division of
                     Human Genetics, Southampton SO16 6YD, UK.
SOURCE:              Human molecular genetics, (2004 Dec 15) 13 (24) 3189-202.
                     Journal code: 9208958. ISSN: 0964-6906.
PUB. COUNTRY:        England: United Kingdom
DOCUMENT TYPE:       Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:            English
FILE SEGMENT:        IN-PROCESS; NONINDEXED; Priority Journals
ENTRY DATE:          Entered STN: 20041204
                     Last Updated on STN: 20050122
AB   We show that the allele-dependent expression of transcripts encoding
     soluble HLA-DQbeta chains is determined by branchpoint sequence (BPS)
     haplotypes in DQB1 intron 3.  BPS RNAs associated with low inclusion of
     the transmembrane exon in mature transcripts showed impaired binding to
     splicing factor 1 (SF1), indicating that alternative splicing of DQB1 is
     controlled by differential BPS recognition early during spliceosome
     assembly.  We also demonstrate that naturally occurring human BPS point
     mutations that alter splicing and lead to recognizable phenotypes cluster
     in BP and in position -2 relative to BP, implicating impaired SF1-BPS
     interactions in  ***disease***  -associated BPS substitutions.  Coding
     DNA variants produced smaller fluctuations of  ***exon***
       ***inclusion***  levels than random exonic substitutions, consistent with
     a selection against coding mutations that alter their own exonization.
     Finally, proximal splicing in this multi-allelic reporter system was
     promoted by at least seven  ***SR***  ***proteins***  and repressed
     by hnRNPs F, H and I, supporting an extensive antagonism of factors
     balancing the splice site selection.  These results provide the molecular
     basis for the haplotype-specific expression of soluble DQbeta, improve
     prediction of intronic point mutations and indicate how extraordinary,
     selection-driven DNA variability in HLA affects pre-mRNA splicing.

L15  ANSWER 2 OF 6     MEDLINE on STN
ACCESSION NUMBER:    2003297183     MEDLINE
DOCUMENT NUMBER:     PubMed ID: 12824367
```

TITLE: ESEfinder: A web resource to identify exonic splicing enhancers.
AUTHOR: Cartegni Luca; Wang Jinhua; Zhu Zhengwei; Zhang Michael Q; Krainer Adrian R
CORPORATE SOURCE: Cold Spring Harbor Laboratory, Cold Spring Harbor, NY 11724, USA.
CONTRACT NUMBER: CA88351 (NCI)
GM42699 (NIGMS)
HG01696 (NHGRI)
SOURCE: Nucleic acids research, (2003 Jul 1) 31 (13) 3568-71.
Journal code: 0411011. ISSN: 1362-4962.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200308
ENTRY DATE: Entered STN: 20030626
Last Updated on STN: 20030819
Entered Medline: 20030818

AB Point mutations frequently cause genetic ***diseases*** by disrupting the correct pattern of pre-mRNA splicing. The effect of a point mutation within a coding sequence is traditionally attributed to the deduced change in the corresponding amino acid. However, some point mutations can have much more severe effects on the structure of the encoded protein, for example when they inactivate an exonic splicing enhancer (ESE), thereby resulting in ***exon*** ***skipping*** . ESEs also appear to be especially important in exons that normally undergo alternative splicing. Different classes of ESE consensus motifs have been described, but they are not always easily identified. ESEfinder (http://exon.cshl.edu/ESE/) is a web-based resource that facilitates rapid analysis of exon sequences to identify putative ESEs responsive to the human ***SR*** ***proteins*** SF2/ ***ASF*** , SC35, SRp40 and SRp55, and to predict whether exonic mutations disrupt such elements.

L15 ANSWER 3 OF 6 MEDLINE on STN
ACCESSION NUMBER: 2003045519 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12524529
TITLE: Correction of disease-associated exon skipping by synthetic exon-specific activators.
COMMENT: Comment in: Nat Struct Biol. 2003 Mar;10(3):147. PubMed ID: 12605214
Comment in: Trends Biotechnol. 2003 Aug;21(8):328-30. PubMed ID: 12902166
Comment in: Trends Mol Med. 2003 Jun;9(6):229-32; discussion 233-4. PubMed ID: 12829008
AUTHOR: Cartegni Luca; Krainer Adrian R
CORPORATE SOURCE: Cold Spring Harbor Laboratory, New York 11724, USA.
SOURCE: Nature structural biology, (2003 Feb) 10 (2) 120-5.
Journal code: 9421566. ISSN: 1072-8368.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200302
ENTRY DATE: Entered STN: 20030130
Last Updated on STN: 20030226
Entered Medline: 20030225

AB Differential exon use is a hallmark of alternative splicing, a prevalent mechanism for generating protein isoform diversity. Many ***disease*** -associated mutations also affect pre-mRNA splicing, usually causing inappropriate ***exon*** ***skipping*** . ***SR*** ***proteins*** are essential splicing factors that recognize exonic splicing enhancers and drive ***exon*** ***inclusion*** . To emulate this function of ***SR*** ***proteins*** , we designed small chimeric effectors comprising a minimal synthetic RS domain covalently linked to an antisense moiety that targets an exon by Watson-Crick base pairing. Here we show that such synthetic effectors can mimic the functions of ***SR*** ***proteins*** and specifically restore wild type splicing when directed to defective BRCA1 or SMN2 pre-mRNA transcripts. This general approach can be used as a tool to investigate splicing mechanisms and modulate alternative splicing of specific genes, and as a therapeutic strategy to correct splicing defects responsible for numerous ***diseases*** .

L15 ANSWER 4 OF 6 MEDLINE on STN
ACCESSION NUMBER: 2002192576 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11925564

TITLE: Disruption of an SF2/ASF-dependent exonic splicing enhancer in SMN2 causes spinal muscular atrophy in the absence of SMN1.
AUTHOR: Cartegni Luca; Krainer Adrian R
CORPORATE SOURCE: Cold Spring Harbor Laboratory, Cold Spring Harbor, New York 11724, USA.
SOURCE: Nature genetics, (2002 Apr) 30 (4) 377-84.
Journal code: 9216904. ISSN: 1061-4036.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200205
ENTRY DATE: Entered STN: 20020403
Last Updated on STN: 20020503
Entered Medline: 20020502

AB Alteration of correct splicing patterns by disruption of an exonic splicing enhancer may be a frequent mechanism by which point mutations cause genetic ***diseases*** . Spinal muscular atrophy results from the lack of functional survival of motor neuron 1 gene (SMN1), even though all affected individuals carry a nearly identical, normal SMN2 gene. SMN2 is only partially active because a translationally silent, single-nucleotide difference in exon 7 causes ***exon*** ***skipping*** . Using ESE motif-prediction tools, mutational analysis and in vivo and in vitro splicing assays, we show that this single-nucleotide change occurs within a heptamer motif of an exonic splicing enhancer, which in SMN1 is recognized directly by SF2/ ***ASF*** . The abrogation of the SF2/ ***ASF*** -dependent ESE is the basis for inefficient inclusion of exon 7 in SMN2, resulting in the spinal muscular atrophy phenotype.

L15 ANSWER 5 OF 6 MEDLINE on STN
ACCESSION NUMBER: 2000492526 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10979205
TITLE: Repression of aberrant splicing in human beta-globin pre-mRNA with HbE mutation by antisense oligoribonucleotide or splicing factor SF2/ASF.
AUTHOR: Shirohzu H; Yamaza H; Fukumaki Y
CORPORATE SOURCE: Division of Disease Genes, Kyushu University, Fukuoka, Japan.
SOURCE: International journal of hematology, (2000 Jul) 72 (1) 28-33.
Journal code: 9111627. ISSN: 0925-5710.
PUB. COUNTRY: Ireland
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200010
ENTRY DATE: Entered STN: 20001027
Last Updated on STN: 20001027
Entered Medline: 20001017

AB Hemoglobin (Hb) E is the most common Hb variant among Southeast Asian populations. The mutation in codon 26 (GAG to AAG) of the beta-globin gene (beta E) induces alternative splicing, resulting in the production of normally and aberrantly spliced beta-globin mRNA. Compound heterozygosity for beta-thalassemia and HbE, beta-thalassemia/HbE ***disease*** , could lead to a severe thalassemia phenotype. Repression of ***aberrant*** ***splicing*** from the beta E mutation could ameliorate the severity in such patients. We showed that the ***aberrant*** ***splicing*** was partially repressed in cells treated with antisense oligoribonucleotide targeted to the aberrant 5' splice site. The maximum effect of the antisense oligoribonucleotide was observed at a concentration of 0.4 mumol/L, 36 hours after the treatment in our experiment. We also analyzed the effect of the transient and stable expression of SF2/ ***ASF*** on ***aberrant*** ***splicing*** in cells expressing the beta E-globin gene. Partial repression of the ***aberrant*** ***splicing*** was also observed in both expression systems. Our results imply that antisense oligoribonucleotide treatment and SF2/ ***ASF*** expression are possible therapeutic applications for beta-thalassemia/HbE ***disease*** .

L15 ANSWER 6 OF 6 MEDLINE on STN
ACCESSION NUMBER: 1999308586 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10380879
TITLE: Stage-specific changes in SR splicing factors and alternative splicing in mammary tumorigenesis.

AUTHOR: Stickeler E; Kittrell F; Medina D; Berget S M
CORPORATE SOURCE: Verna and Marrs McLean Department of Biochemistry, Baylor College of Medicine, Houston, Texas 77030, USA.
CONTRACT NUMBER: CA 47112 (NCI)
SOURCE: Oncogene, (1999 Jun 17) 18 (24) 3574-82.
Journal code: 8711562. ISSN: 0950-9232.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199907
ENTRY DATE: Entered STN: 19990715
Last Updated on STN: 19990715
Entered Medline: 19990706

AB Using a mouse model of mammary gland development and tumorigenesis we examined changes in both alternative splicing and splicing factors in multiple stages of mammary cancer. The emphasis was on the SR family of splicing factors known to influence alternative splicing in a wide variety of genes, and on alternative splicing of the pre-mRNA encoding CD44, for which alternative splicing has been implicated as important in a number of human cancers, including breast cancer. We observed step-wise increases in expression of individual ***SR*** ***proteins*** and alternative splicing of CD44 mRNA during mammary gland tumorigenesis. Individual preneoplasias differed as to their expression patterns for ***SR*** ***proteins*** , often expressing only a sub-set of the family. In contrast, tumors demonstrated a complex pattern of SR expression. Little difference was observed between neoplasias and their metastases. Alternative splicing of CD44 also changed through the ***disease*** paradigm such that tumors produced RNA containing a mixture of variable exons, whereas preneoplasias exhibited a more restricted ***exon*** ***inclusion*** pattern. In contrast, other standard splicing factors changed little in either concentration or splicing pattern in the same cells. These data suggest alterations in relative concentrations of specific splicing factors during early preneoplasia that become more pronounced during tumor formation. Given the ability of ***SR*** ***proteins*** to affect alternative processing decisions, our results suggest that a number of pre-mRNAs may undergo changes in alternative splicing during the early and intermediate stages of mammary cancer.

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=> s kerem b?/au
L16          389 KEREM B?/AU

=> d his

     (FILE 'HOME' ENTERED AT 07:38:02 ON 11 FEB 2005)

     FILE 'MEDLINE, CAPLUS, BIOSIS, EMBASE, SCISEARCH, AGRICOLA' ENTERED AT
     07:38:25 ON 11 FEB 2005
L1           3729 S (ALTERNATIVE SPLICING FACTOR) OR ASF
L2           3377 S SR PROTEIN
L3            447 S (HETEROGENEOUS NUCLEAR RIBONUCLEOPROTEIN A1) OR HBRNPA1
L4            220 S E4-ORF3 OR E4-ORF6
L5           7007 S L1 OR L2 OR L3 OR L4
L6           2113 S ABERRANT SPLICING
L7           3455 S (EXON INCLUSION) OR (EXON SKIPPING)
L8           5398 S L6 OR L7
L9             20 S CYCTIC FIBROSIS
L10        103175 S CYSTIC FIBROSIS
L11            19 S L5 (P) L8 (P) L10
L12             4 DUPLICATE REMOVE L11 (15 DUPLICATES REMOVED)
L13            43 S L5 (P) L8 (P) DISEASE
L14             9 DUPLICATE REMOVE L13 (34 DUPLICATES REMOVED)
L15             6 S L14 NOT L12
L16           389 S KEREM B?/AU

=> s l16 and l8
L17             8 L16 AND L8

=> duplicate remove l17
DUPLICATE PREFERENCE IS 'MEDLINE, CAPLUS, BIOSIS, EMBASE, SCISEARCH'
KEEP DUPLICATES FROM MORE THAN ONE FILE?  Y/(N):n
PROCESSING COMPLETED FOR L17
L18             4 DUPLICATE REMOVE L17 (4 DUPLICATES REMOVED)

=> s l16 and l5
```

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L19             7 L16 AND L5

=> duplicate remove l19
DUPLICATE PREFERENCE IS 'MEDLINE, CAPLUS, BIOSIS, EMBASE, SCISEARCH'
KEEP DUPLICATES FROM MORE THAN ONE FILE?  Y/(N):n
PROCESSING COMPLETED FOR L19
L20             3 DUPLICATE REMOVE L19 (4 DUPLICATES REMOVED)

=> s l18 or l20
L21             5 L18 OR L20

=> d l21 1-5 ibib abs

L21  ANSWER 1 OF 5     MEDLINE on STN
ACCESSION NUMBER:    2001014733     MEDLINE
DOCUMENT NUMBER:     PubMed ID: 10915765
TITLE:               Cellular and viral splicing factors can modify the splicing
                     pattern of CFTR transcripts carrying splicing mutations.
AUTHOR:              Nissim-Rafinia M; Chiba-Falek O; Sharon G; Boss A;
                       ***Kerem B***
CORPORATE SOURCE:    Department of Genetics, Life Sciences Institute, The Hebrew
                     University, Jerusalem 91904, Israel.
SOURCE:              Human molecular genetics, (2000 Jul 22) 9 (12) 1771-8.
                     Journal code: 9208958. ISSN: 0964-6906.
PUB. COUNTRY:        ENGLAND: United Kingdom
DOCUMENT TYPE:       Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:            English
FILE SEGMENT:        Priority Journals
ENTRY MONTH:         200010
ENTRY DATE:          Entered STN: 20010322
                     Last Updated on STN: 20021218
                     Entered Medline: 20001027
AB   Variable levels of aberrantly spliced cystic fibrosis transmembrane
     conductance regulator (CFTR ) transcripts were suggested to correlate with
     variable cystic fibrosis (CF) severity.  We studied the effect of the
     cellular splicing factors, hnRNP A1 and   ***ASF***  /SF2, and their
     adenoviral analogues,   ***E4***  -  ***ORF6***   and   ***E4***  -
       ***ORF3***   , that promote   ***exon***     ***skipping***   and/or
       ***exon***     ***inclusion***   , on the splicing pattern of the CFTR
     mutation 3849+10kb C-->T and the 5T allele.  These mutations can lead to
     cryptic   ***exon***     ***inclusion***   and   ***exon***
       ***skipping***   , respectively.  Overexpression of the cellular factors
     promoted   ***exon***     ***skipping***   of pre-mRNA transcribed from
     minigenes carrying the mutation (p5T or p3849M).  This led to a
     substantial decrease in the level of correctly spliced mRNA transcribed
     from p5T and generated correctly spliced mRNA transcribed from p3849M that
     was not found without overexpression of the factors.  The viral factor,
       ***E4***  -  ***ORF3***   , promoted   ***exon***     ***inclusion***   and
     led to a substantial increase of the correctly spliced mRNA transcribed
     from the p5T.  The factor,   ***E4***  -  ***ORF6***   , activated
       ***exon***     ***skipping***   and generated correctly spliced mRNA
     transcribed from p3849M.  Thus, overexpression of   ***alternative***
       ***splicing***     ***factors***   can modulate the splicing pattern of
     CFTR alleles carrying splicing mutations.  These results are important for
     understanding the mechanism underlying phenotypic variability in CF and
     other genetic diseases.

L21  ANSWER 2 OF 5     MEDLINE on STN
ACCESSION NUMBER:    1998029368     MEDLINE
DOCUMENT NUMBER:     PubMed ID: 9363081
TITLE:               The relationship between genotype and phenotype in cystic
                     fibrosis.
AUTHOR:              Kerem E;   ***Kerem B***
CORPORATE SOURCE:    Department of Pediatrics, Pulmonary and Cystic Fibrosis
                     Clinic, Shaare Zedek Medical Center, Jerusalem, Israel.
SOURCE:              Current opinion in pulmonary medicine, (1995 Nov) 1 (6)
                     450-6.  Ref: 46
                     Journal code: 9503765. ISSN: 1070-5287.
PUB. COUNTRY:        United States
DOCUMENT TYPE:       Journal; Article; (JOURNAL ARTICLE)
                     General Review; (REVIEW)
                     (REVIEW, TUTORIAL)
LANGUAGE:            English
FILE SEGMENT:        Priority Journals
ENTRY MONTH:         199712
ENTRY DATE:          Entered STN: 19980109
                     Last Updated on STN: 19980109
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Entered Medline: 19971205

AB Cystic fibrosis is characterized by a wide variability of clinical expression. The cloning of the cystic fibrosis transmembrane conductance regulator gene and the identification of its mutations has promoted extensive research into the association between genotype and phenotype. Several studies showed that there are mutations, such as delta F508 (the most common mutation worldwide), that are associated with a severe phenotype: early age at diagnosis, pancreatic insufficiency, poor nutritional status, high incidence of meconium ileus, and high sweat chloride levels; lung disease, however, is variable. The milder mutation is dominant over the severe mutation causing a milder phenotype. In vitro studies of cystic fibrosis transmembrane conductance regulator function suggested that different mutations cause different defects of protein production and function. Five mechanisms by which mutations disrupt cystic fibrosis transmembrane conductance regulator function have been suggested: class I mutations cause defective protein production, class II mutations are associated with defective protein processing, class III mutations are associated with defective regulation, class IV mutations are associated with defective conductance, and class V mutations include mutations affecting the level of normal messenger RNA transcript and protein required for normal function. This class might include mutations affecting correct splicing of pre-messenger RNA transcripts by either ***exon*** ***skipping*** or by inclusion of extra cryptic exons.

L21 ANSWER 3 OF 5 CAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2002:123508 CAPLUS
DOCUMENT NUMBER: 136:162403
TITLE: Control of aberrant gene expression by ***alternative*** ***splicing*** ***factor***
INVENTOR(S): ***Kerem, Batsheva***
PATENT ASSIGNEE(S): Yissum Research Development Company of the Hebrew University of Jerusalem, Israel
SOURCE: U.S. Pat. Appl. Publ., 15 pp., Cont.-in-part of U.S. Ser. No. 421,891, abandoned.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2002018768	A1	20020214	US 2001-871809	20010604
PRIORITY APPLN. INFO.:			US 1999-421891	B2 19991021

AB The invention concerns a method for treating various genetic diseases caused by ***aberrant*** ***splicing*** by utilizing factors which can modulate alternative splicing. The method of the present invention is esp. suitable for the treatment of cystic fibrosis.

L21 ANSWER 4 OF 5 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation. on STN

ACCESSION NUMBER: 2002:23323 BIOSIS
DOCUMENT NUMBER: PREV200200023323
TITLE: The effect of cellular and viral splicing factors on the level of normal CFTR RNA.
AUTHOR(S): Nissim-Rafinia, M. [Reprint author]; ***Kerem, B.*** [Reprint author]
CORPORATE SOURCE: Dept Genetics, Hebrew Univ, Jerusalem, Israel
SOURCE: American Journal of Human Genetics, (October, 2001) Vol. 69, No. 4 Supplement, pp. 650. print.
Meeting Info.: 51st Annual Meeting of the American Society of Human Genetics. San Diego, California, USA. October 12-16, 2001.
CODEN: AJHGAG. ISSN: 0002-9297.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
Conference; (Meeting Poster)
LANGUAGE: English
ENTRY DATE: Entered STN: 26 Dec 2001
Last Updated on STN: 25 Feb 2002

L21 ANSWER 5 OF 5 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation. on STN

ACCESSION NUMBER: 1995:477734 BIOSIS
DOCUMENT NUMBER: PREV199598492034
TITLE: Variable levels of aberrantly spliced CFTR mRNA transcribed from the 5T allele: The cause for variable disease severity among individuals and between organs of the same individual.

AUTHOR(S): ***Kerem, B.*** [Reprint author]; Rave-Harel, N. [Reprint author]; Nissim-Rafinia, M. [Reprint author]; Goshen, R.; Madgar, I.; Augarten, A.; Kerem, E.
CORPORATE SOURCE: Dep. Genet., Hebrew Univ., Jerusalem, Israel
SOURCE: American Journal of Human Genetics, (1995) Vol. 57, No. 4 SUPPL., pp. A244.
Meeting Info.: 45th Annual Meeting of the American Society of Human Genetics. Minneapolis, Minnesota, USA. October 24-28, 1995.
CODEN: AJHGAG. ISSN: 0002-9297.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
Conference; (Meeting Poster)
LANGUAGE: English
ENTRY DATE: Entered STN: 1 Nov 1995
Last Updated on STN: 1 Nov 1995

=> d his

(FILE 'HOME' ENTERED AT 07:38:02 ON 11 FEB 2005)

FILE 'MEDLINE, CAPLUS, BIOSIS, EMBASE, SCISEARCH, AGRICOLA' ENTERED AT 07:38:25 ON 11 FEB 2005

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L1          3729 S (ALTERNATIVE SPLICING FACTOR) OR ASF
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L19            7 S L16 AND L5
L20            3 DUPLICATE REMOVE L19 (4 DUPLICATES REMOVED)
L21            5 S L18 OR L20
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=> log y

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